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Subcellular Trafficking of the Amyloid Precursor Protein Gene Family and Its Pathogenic Role in Alzheimer's Disease

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Key Words
Axonal transport · Kinesin · c-Jun N-terminal kinase-interacting protein · Cargo receptor

Abstract
Changes in the intracellular transport of amyloid precursor protein (APP) affect the extent to which APP is exposed to α- or β-secretase in a common subcellular compartment and therefore directly influence the degree to which APP undergoes the amyloidogenic pathway leading to generation of β-amyloid. As the presynaptic regions of neurons are thought to be the main source of β-amyloid in the brain, attention has been focused on axonal APP trafficking. APP is transported along axons by a fast, kinesin-dependent anterograde transport mechanism. Despite the wealth of in vivo and in vitro data that have accumulated regarding the connection of APP to kinesin transport, it is not yet clear if APP is coupled to its specific motor protein via an intracellular interaction partner, such as the c-Jun N-terminal kinase-interacting protein, or by yet another unknown molecular mechanism. The cargo proteins that form a functional complex with APP are also unknown. Due to the long lifespan, and vast extent, of neurons, in particular axons, neurons are highly sensitive to changes in subcellular transport. Recent in vitro and in vivo studies have shown that variations in APP or tau affect mitochondrial and synaptic vesicle transport. Further, it was shown that this axonal dysfunction might lead to impaired synaptic plasticity, which is crucial for neuronal viability and function. Thus, changes in APP and tau expression may cause perturbed axonal transport and changes in APP processing, contributing to cognitive decline and neurodegeneration in Alzheimer's disease.

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Subcellular Trafficking of APP/APLPs

The amyloid precursor protein (APP), similar to other typical type I transmembrane proteins, is cotranslationally translocated during migration across the ER membrane and remains anchored there by a single membrane spanning α-helical region. APP is inserted in the membrane such that only a short tail remains in the cytosol, whereas the major N-terminal forms a relatively large extracellular domain. APP is then transported from the ER to the Golgi apparatus, whereby it undergoes different posttranslational covalent modifications, including N- and O-glycosylation, sialylation, and modification with chondroitin sulfate glycosaminoglycan and/or dermatan sulfate glycosaminoglycan [1, 2]. During passage through the different subcompartments of the Golgi apparatus, APP is sorted into secretory vesicles. On its way from the Golgi to the plasma membrane and to endosomes, a portion of APP is processed by different secretases. The extracellular domain of APP can be cleaved by α-secretase or, alternatively, by the β-secretase BACE 1 (β-site APP cleaving enzyme 1). The resulting membrane-retained

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C-terminal fragments are subsequently processed by cleavage within the transmembrane region by the γ-secretase complex [3]. β- and γ-cleavage of APP results in the release of amyloid-β (Aβ) peptides, while α- and γ-cleavage generate p3 fragments. Besides the Golgi apparatus, the plasma membrane was shown to be one of the two major sites where α-secretase cleavage of APP takes place [4, 5]. In contrast, BACE1 is most active at mildly acidic pH [6], making endosomes the most likely location for BACE cleavage of APP. Moreover, BACE 1 was reported to cycle between the cell surface and endosomes [7]. It was also shown that internalization of cell surface APP via endocytosis leads to elevated Aβ generation and subsequent release into the medium [8]. Thus, changes in subcellular APP trafficking affect the time that APP spends together with α- or β-secretase in a common subcellular compartment and, thereby, the APP processing.

In particular, neurons, which have very long processes (the axon of human motoneurons can be up to 1 m in length), are dependent on an appropriate subcellular localization of transcripts and proteins which presumes a highly complex transport system. Due to their morphology and long life span, neurons are highly vulnerable to any perturbation of their transport machinery. There is emerging evidence that impaired axonal transport is causal for different neurodegenerative disorders, including Alzheimer's disease (AD).

APP is anterogradely transported in tubular vesicles along the axons [9–15] with a velocity up to 10 μm per second [16, 17]. These transport vesicles differ from axonal vesicles transporting neurotransmitters towards the synapse [18] or from those much slower vesicles, transporting synaptophysin along the axon [17]. The anterograde transport of APP depends on kinesin-1 [2, 9, 17, 19–22], which consists of two kinesin heavy and light chains (KHC, KLC). Motor activity and specificity of cargo binding are localized in the KHC [23], whereas the KLC is thought to regulate the motor activity and bind via its TPR-like motif to vesicular receptor and linker proteins. In mammals, there are three different KHCs: kinesin-1A, -1B and -1C (KIF5A, B, C) [24–28], and three KLCs [29], KLC1, KLC2 and KLC3. Kinesin-1A, kinesin-1C and KLC1 are specific to neurons, whereas kinesin-1B and KLC2 are expressed ubiquitously [24, 25]. The KLC3 expression in the brain is very low, but it plays a unique role in the spermatids in testis [30]. Different kinesin-1 tetrameric heterocomplexes consisting of two KHCs and two KLCs may participate in selective transport by using adapter or scaffolding proteins to recognize and bind specific cargoes [31].

It was proposed that APP may play a role as a kinesin cargo receptor [32], directly interacting with the motor protein kinesin-1, connecting it to a certain axonal vesicle class with specific cargo proteins, including the APP secretases, BACE and presinilin (PS) [33]. Aβ production was observed in sciatic nerve extracts, indicating that APP may be processed in axonal transport vesicles [33].

The hypothesis that the APP intracellular domain (AICD) interacts directly with kinesin-1 was based on GST pull-down analyses, showing high affinity binding (K_D = 16–18 nM) of GFP-AICD with GST-KLC1 and GST-KLC2 fusion proteins. More detailed GST pull-down experiments revealed that this binding was caused by a non-specific hydrophobic interaction to the tandem repeats in the carboxy terminus of bacterially expressed KLC1 [34]. Consistent with this, GST pull-down analyses with GST-AICD and recombinant KLC1 expressed in mammalian cells revealed no specific interaction, whereas other known interaction partners of APP, such as Fe65 or Numb, were specifically retained on beads loaded with GST-AICD. Together, these data strongly suggest that KLC1 does not interact directly with the cytoplasmic tail of APP. Nonetheless, KLC1 and KLC2 appear to be associated with different subsets of APP-containing membrane compartments [S.K., pers. obs.; 32]. Thus, an indirect interaction of APP with kinesin via a cytosolic APP interaction partner could be postulated. However, coimmunoprecipitation studies of APP and kinesin-1 from mouse brain lysates with any of a wide range of specific antibodies to different epitopes on KLC, KHC, and APP N- and C-terminus (kindly obtained from G. Multhaup, Berlin, and T. Hartmann, Heidelberg) [34; S.K., pers. commun.] revealed, in contrast to previous studies from Kamal et al. [32], no indication for a common complex of APP and kinesin. Importantly, other putative kinesin-cargo receptors, such as JIP3/JSAP1 (Sunday driver, Syd) [35], have been coimmunoprecipitated under identical conditions [34]. Nevertheless, based on the negative results from the in vitro binding studies and coimmunoprecipitation studies, an indirect association of APP to kinesin-1 via an AICD interacting protein cannot be excluded.

Different linker molecules are known that connect a specific motor protein to a certain class of vesicles. For example, β1 adaptin was reported to couple KIF13A, a plus end-directed microtubule-dependent motor protein, to the AP-1 adaptor complex and mannnose-6-phosphate receptor [36]. Other linker proteins are scaffolding proteins that are capable of interacting with a set of different interaction partners and which often cluster functional complexes, such as PSD-95 [37], glutamate-receptor-in-

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Table 1. Different linker molecules connect specific motor protein to certain class of vesicles

Motorprotein	Motorprotein new nomenclature [28]	Linker	Cargo	References
KHC	Kinesin-1	Syntabulin-α	Syntaxin-1, mitochondria	[84, 85]
KIF5	Kinesin-1	GRIP1	AMPA receptor	[38, 40]
KIF5	Kinesin-1	JIP1,2,3 (MAPK8IP1, 2, 3)	JNK signaling cascade (DLK), ApoER2	[34, 35, 45–51]
KIF3A	Kinesin-2	–	Opsin, arrestin	[86]
KIF3, KAP	Kinesin-2	–	Chromosomes, flagellar cargoes	[87–90]
KIF13A	Kinesin-3	AP-1	clathrin, M6PR	[36]
KIF17	Kinesin-3	X11 (mLIN-10, MINT)	mLIN-2 (CASK), mLIN-7 (VELIS/ MALS), NMDAR (NR2B subunit)	[43, 44]
KIF1A	Kinesin-3A	Liprin-α, (PPFIA2)	GRIP, AMPAR, RIM, GIT1, βPIX, synaptic vesicles	[39, 41, 42, 91]
KIF1B	Kinesin-3B	PSD-95 (SAP90)	PSD-95, synaptic precursor vesicles	[37, 92]

PPFIA2 = Protein-tyrosine phosphatase, receptor-type, F polypeptide-interacting protein α2; PSD-95 = postsynaptic density 95; SAP90 = synapse-associated protein 90; GRIP1 = glutamate receptor-interacting protein 1; AP-1 = adaptor protein 1; mLIN-10 = vertebrate LIN10 homolog; MINT = MUNC18-1-interacting protein; NMDAR = N-methyl-D-aspartate receptor; CASK = calcium/calmodulin-dependent serine protein kinase; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolpropionate; GRK = G-protein-coupled receptor kinase; GIT1 = GRK-interacting protein 1; PAK = p21-activated kinase and phospholipase C-interacting protein 1; PIX = PAK-interacting exchange factor; M6PR = mannnose-6-phosphate receptor.

teracting protein 1 [38–42], X11 (LINs, MINT) [43, 44], Syd, a c-Jun N-terminal kinase (JNK)-interacting protein (JIP) 3 homologue in *Drosophila* or JIP1b and JIP2 [34, 35, 45–51] (table 1).

X11 and JIP1b/2 have a phosphotyrosine interaction/binding domain [52–54] that interacts with the NPTY motif of AICD. Thus, they may couple APP-containing vesicles to a certain signaling pathway by creating a scaffold [52–54] and may link APP to a special type of kinesin transport. Considering that APP is driven with different velocities (2–10 μm/s), the different linker proteins may couple APP to different kinesin transport complexes with different velocity characteristics. Each of these adapter proteins could represent the unknown linker protein for a specific subset of vesicles.

Based on in vitro analyses it was proposed that JIP-1b might connect APP-bearing axonal vesicles to the kinesin-1 motor mechanism [46, 47, 50]. To test this proposal in vivo, we performed APP/JIP1b coimmunoprecipitation studies and analyzed the subcellular transport of APP in primary neurons treated with specific siRNA to knockdown JIP-1b/2. Under conditions that allowed specific coimmunoprecipitation of complexes containing APP and APLP1 or APLP2 [55], coimmunoprecipitation of APP and JIP-1b was not observed. However, these data do not exclude a role of JIP-1b as a linker of APP to the transport machinery, which might require only a transient, low affinity binding. To address the influence of JIP1b on APP trafficking more directly, we screened different siRNAs directed against JIP1b and found that in mixed cortical primary neurons (DIV11) a knockdown of endogenous JIP-1b to less than 5% of the endogenous level (fig. 1) was observed after siRNA treatment. Immunocytochemical analyses of wild-type neurons with anti-JIP1b antibodies revealed that endogenous JIP1b accumulated at the tips of the neurites (fig. 2a–c). In JIP-1b knockdown neurons, no specific JIP1b immunoreactivity was detected (fig. 2d–e). Surprisingly, costaining of JIP-1b siRNA-treated neurons with anti-APP antibodies revealed that APP was localized not just in the perinuclear region, but also at the tips of neurites, showing that APP can be anterogradely transported in the absence of JIP1b (fig. 2d, f). These data are consistent with the results from a recent study, showing that the majority of APP does not colocalize with JIP-1b and that a knockdown of JIP1b only has an influence on transport of the minor pool of APP phosphorylated at

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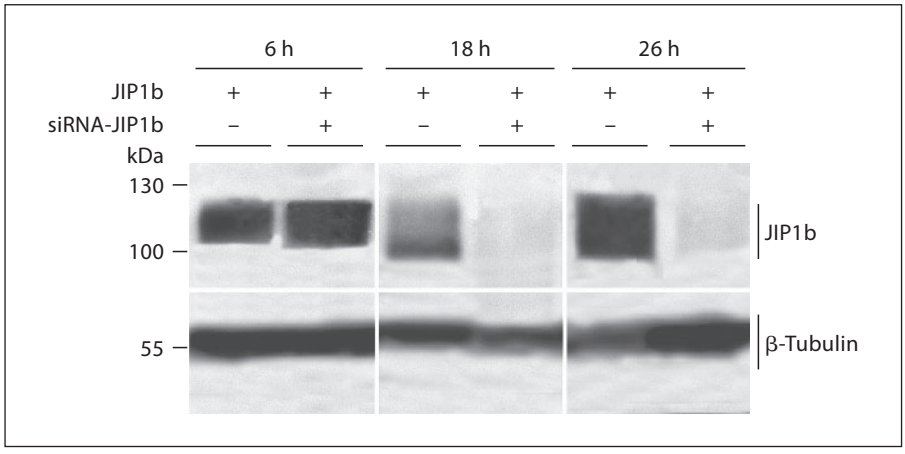

Fig. 1. JIP-1b knockdown in primary neurons. Mouse primary neurons (DIV11) were transfected with JIP-1b cDNA only or simultaneously treated with 40 nM siRNA against JIP1b. Expression of JIP1b was evaluated 6–24 h after transfection. The cells were lysed and subjected to PAGE and Western blot analyses using anti-JIP-1b [1:500] antibody. Anti-β-tubulin [1:10,000] antibody was used as a loading control. Efficient knockdown of JIP-1b occurs after 18 h up to 24 h.

threonin 668 [49]. Altogether, it is clear that APP does not bind directly to kinesin and that JIP1b is not the main linker that couples APP to the anterograde transport machinery (fig. 3). However, further analyses are necessary to determine the molecular link between APP and the kinesin motor mechanism.

The molecular composition of APP/APLPs-containing vesicles also remains unclear. BACE and PS1 are transported along the axon [56, 57] and, as mentioned before, Kamal et al. [33] proposed that these two APP secretases are specific cargoes of APP-containing vesicles transported by the fast anterograde transport machinery. However, careful studies assessing the trafficking of membrane proteins in the sciatic nerves of mice with heterozygous or homozygous deletions of APP show that the axonal transport kinetics of BACE and PS1 are different from APP and that they are unchanged in APP knockout mice [34]. These data argue that the APP-processing apparatus is transported in TGN vesicles different from those that transport APP, suggesting axonal processing of APP by BACE and the γ-secretase complex takes place at the plasma membrane or endosomes. However, it is not clear whether α-secretase might be cotransported with APP. Other proposed cargo proteins cotransported with APP have not been verified in subsequent studies [33, 34].

In recent studies from our laboratory, we determined that APP, APLP1 and APLP2 not only have very similar structures, but also form homo- and heterotypic complexes, suggesting a close functional relation between the APP gene family members [55]. This view is also supported by genetic analyses of the APP gene family [58, 59] and studies addressing the influence of APLP1 and APLP2 on APP processing [60]. We could show in extensive coimmunoprecipitation studies that both mature and immature APP/APLPs can interact with similar efficiency [55]. This observation is consistent with studies showing in vitro dimerization of recombinantly expressed soluble APP [61]. However, we found that endogenous heterocomplexes contain exclusively mature APP/APLPs. Moreover, these high molecular weight species of APP family interacting proteins strongly accumulate in synaptic plasma membrane fractions [55]. As only mature APP is present at the cell surface [62], we favor a model in which endogenous APP/APLP heterointeraction in the brain is limited to the cell surface, which would allow transcellular binding. APP and APLP2 have previously been shown to be transported to presynaptic terminals [1, 10] and growth cones of neurons [63], while APLP1 has been reported to localize to the postsynapse terminals [64]. Interestingly, all APP family members exhibit developmentally increased expression levels correlating with postembryonic synaptogenesis [13, 65, 66], and recent genetic analyses in mouse and *Drosophila* revealed that the APP gene family members are required for neuromuscular synaptogenesis [67, 68]. Together with our data, these findings indicate that transcellular APP/APLP interaction is part of the regulation of synaptogenesis. In regard to the different subcellular localizations of APP, APLP1 and APLP2 in neurons [1, 64], it is reasonable that APP, APLP1 and APLP2 are transported in different types of vesicles and are differently coupled to specific anterograde transport mechanisms. In principle, each subtype of transport vesicle is thought to mediate the axonal/dendritic transport of a specific set of functional protein complexes [69, 70]. Thus, it will be of

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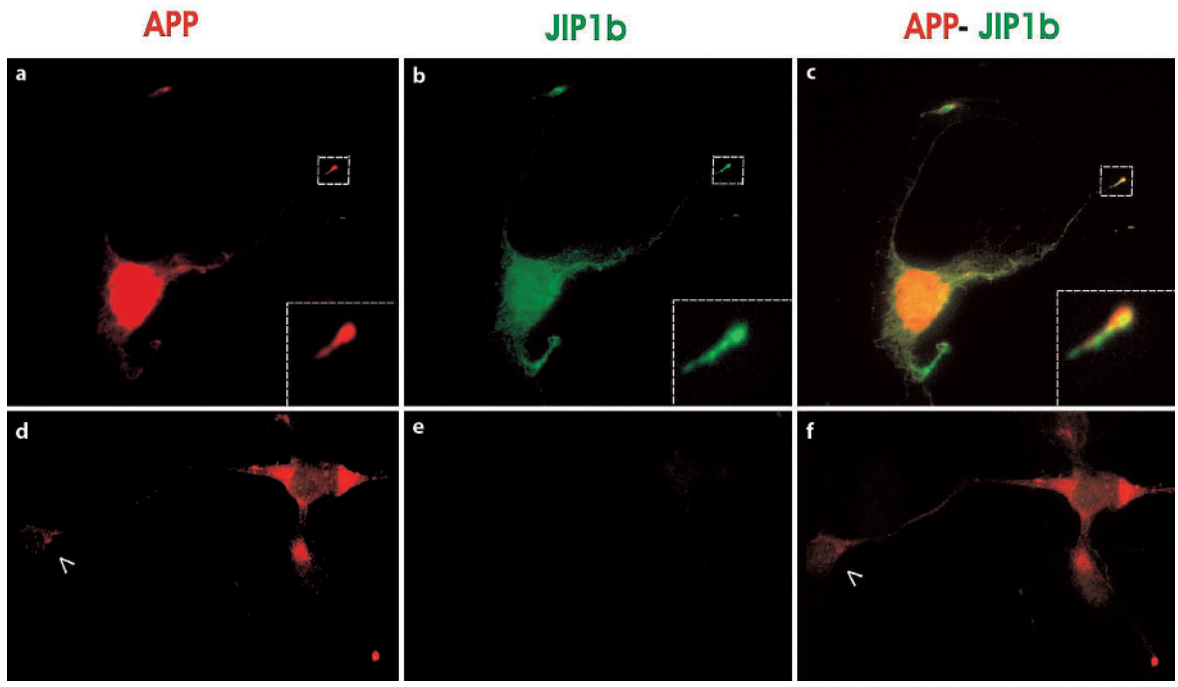

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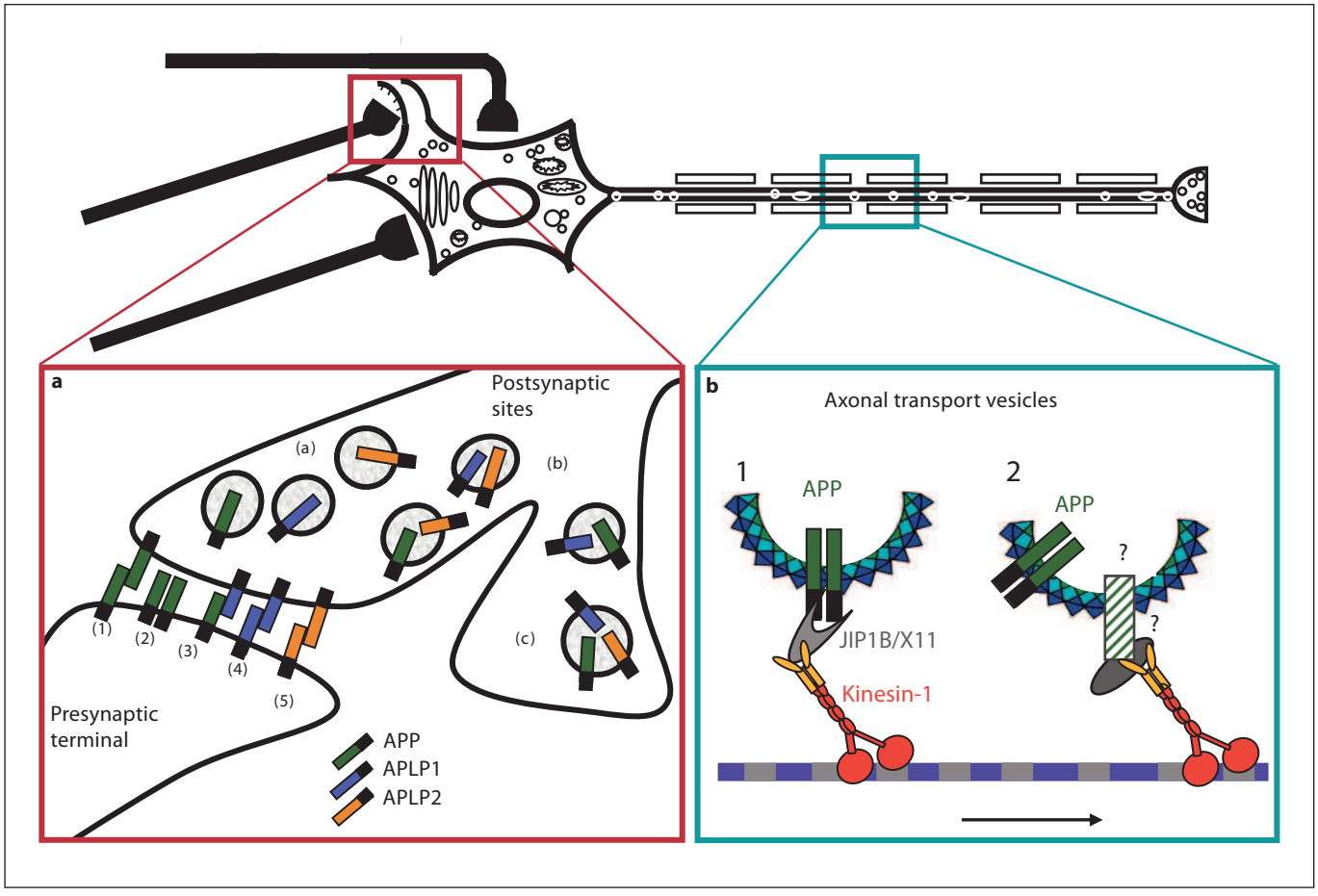

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great interest to elucidate the molecular composition of the specific transport vesicle types transporting APP, APLP1 and APLP2. These analyses will also allow conclusions regarding their specific molecular function (fig. 3).

Pathogenic Role of the APP Gene Family in Axonal Transport

In addition to the importance of interactions between APP and its processing machinery during transport, another potential important role of APP in axonal transport was shown in studies of *Drosophila* wandering third instar larvae with a deletion of the APPL gene (the *Drosophila* homologue of APP) or overexpressing APP/APPL. Changes in the dose of APP/APPL resulted in increased accumulation of synaptic vesicles in peripheral axons – a phenotype also observed in JIP 1/2 (APLIP1) or JIP3/JSAP1 (Syd) mutant *Drosophila* larvae [35, 46, 71]. JIP1 and JIP2 – as well as JIP3, although very different in primary sequence – belong to a family of scaffold factors for the mitogen-activated protein kinase (MAPK) cascades, and accumulate at the leading edges of cells [72–74]. Mutation of APLIP1 caused axonal transport defects of both anterograde and retrograde vesicle transport. Thus, APLIP1 may be an important part of motor-cargo linkage complexes for kinesin-1 and dynein. Alternatively, APLIP1 and its associated JNK signaling proteins may serve as an important signaling module in MAPK pathway for regulating transport by the two opposing mechanisms [46, 75]. APP might function as a regulator of the scaffolding activity of JIP1 in the JNK signaling pathway, as recently shown for the Notch intracellular domain [76].

In a recent paper, Stokin et al. [77] identified axonal defects in APP transgenic mice. They found in fibers of the nucleus basalis of Meynert, which provide the major cholinergic input to the cerebral cortex, that the axonal varicosities exhibited substantial variation in size and morphology. Generally, varicosities correspond to en passant synaptic boutons, are regularly spaced, and have relatively constant diameters. The varicosities in the transgenic mice, in contrast, were often unusually large and irregularly spaced and contained large numbers of mitochondria, sporadic multilamellar bodies, vacuoles, and vesicles. Varicosities of diameters larger than 3 μm, termed swellings, were in transgenic mice three times as many as in controls. This is a feature suggestive of axonal transport defects, as found previously in tau transgenic mouse and *Drosophila* models [78–80] and in dystrophic neuritis embedded in amyloid in AD [80, 81]. Interestingly, a 50% reduction in genetic dosage of KLC1 in these APP transgenic mice caused a significant increase of axonal swellings and Aβ generation preceding the onset of amyloid deposition, suggesting that impaired transport may contribute to early stages of AD [77].

Recently, it was reported that transgenic expression of human tau (0N3R) in *Drosophila* larval motor neurons causes morphological and functional disruption to the neuromuscular junctions [80]. Despite reduction in size with irregular and abnormal bouton structure and abnormal endo-/exocytosis, tau-expressing neuromuscular junctions retain synaptotagmin expression and can form active zones. Electrophysiological studies showed that following high frequency stimulation (50 Hz), evoked synaptic potentials were significantly decreased [80]. The mechanism underlying the change in evoked synaptic potentials is not clear, but might contribute to a significant reduction in the number of mitochondria in the presynaptic terminals of motor neurons expressing mutant tau. These results suggest that disruption of axo-

Fig. 2. The anterograde transport of APP is independent of JIP1b. Mouse primary neurons (DIV5) were treated with JIP1b siRNA (**d–f**) or nonsense siRNA (**a–c**) for control. The cells were subjected to immunocytochemical analyses using anti-APP (**a**, **c**, **d**, **f**; red) and anti-JIP-1b (**b**, **c**, **e**, **f**; green) antibodies 18 h after transfection. Colocalization of endogenous APP (red) and JIP1b (green) was detected in the cell soma and at the tips of neurites, as indicated by the overlap (**c**, **f**; yellow). Scale bar: 20 μm (insets: 6 μm).

Fig. 3. Model of the subcellular transport of the APP family members. APP, APLP1 and APLP2 (APP/APLPs) are transported in neurons to the dendritic and axonal compartment. **a** They are capable of forming homo- and heterocomplexes in a cis- and transcellular fashion (1–5), promoting cell-cell adhesion. It is possible that the transcellular interaction takes place between pre- and postsynaptic membranes in neurons. Alternatively, transcellular interaction involving APP/APLPs may take place between neurons and glia cells. APP/APLPs can be transported in common (b, c) or separate (a) vesicles in the form of monomers, homo- or heterocomplexes, towards the plasma membrane. The different dimer combinations and vesicle compositions may modulate the targeting and functions of APP/APLPs in neurons. **b** Axonal transport of APP/APLPs is driven by kinesin-1. A part of APP/APLPs might be coupled via JIP1b to the motor machinery (1); however, recent data indicate that APP/APLPs can be transported by kinesin in absence of JIP1b, suggesting the existence of an additional molecular linker, coupling APP-containing vesicles to the kinesin motor machinery (2).

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nal transport and synaptic transmission may be key components of the pathogenic mechanism that underlie neuronal dysfunction in the early stages of tauopathies. It will be interesting whether changes in the dose of APP/APPL, which also affect the axonal transport of synaptic vesicles and morphology of synapses in mouse and *Drosophila* models, may also lead to altered synaptic plasticity, thought to represent the neurophysiological correlate of learning and memory [82, 83]. If true, this would strongly favor the hypothesis that changes in the dose of APP and tau cause altered neurotransmission, contributing to cognitive decline and neurodegeneration of AD.

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